CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-248

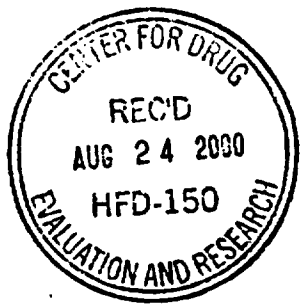
CORRESPONDENCE

cti

Discovery • Treatment • Recovery

T 206.282.7100 F 206.284.6206

REQUEST FOR MEETING AND AMENDMENT TO NEW DRUG APPLICATION:
Labeling Changes



August 24, 2000

Richard Pazdur, M.D., Director,
Division of Oncology Drug Products, FDA, HFD-150
1451 Rockville Pike (Woodmont II Building)
Rockville, MD 20852

Re: **NDA 21-248**
Application for Trisenox™ (arsenic trioxide injection) for the treatment of acute promyelocytic leukemia (APL)

Dear Dr. Pazdur:

Reference is made to Cell Therapeutics, Inc.'s original submission of the New Drug Application (NDA) for Trisenox™ (arsenic trioxide injection) on March 28, 2000. Reference is also made to the Division's proposed Package Insert (dated August 16, 2000) and to a telephone conversation with Dianne Spillman, Project Manager, on August 21, 2000, confirming a meeting with the Division on August 31, 2000 (11:30 am to 12:30 pm).

This letter serves as a formal request for the meeting to discuss the Package Insert changes and also includes **cti**'s changes to the Division's proposed Package Insert of August 16. This amendment consists of the following:

- **Attachment A**:
  - **cti** Package Insert changes (red lined version); please be advised that the red lined version of the package insert will have all changes highlighted except for the Adverse Events table and listing of severe or life threatening events following the table.
  - Justification for changes
  - Clean copy of the changed Package Insert
  - Copy of the FDA Package Insert of August 16, 2000 (for reference)

- **Attachment B**:
  - Proposed Meeting Agenda
  - Issues for Discussion at the August 31, 2000 meeting

We look forward to this important meeting with the Division and appreciate your assistance on the approval of this drug. Please do not hesitate to call if you have questions or need additional information at (206) 270-8424.

Sincerely yours,

Jennie Allewell
Cell Therapeutics, Inc.
Director, Regulatory Affairs and Compliance

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 2	**Date:** September 8, 2000
Re: NDA 21-248 – Follow-up to August 31, 2000 meeting: Complete Responders	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

During the August 31, 2000 labeling meeting, CTI expressed concern that some patients who were complete responders may not have been counted as such in the FDA review.

Attached is our response to this concern.

Sincerely,
/S/
Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150 /Div Files
/D. Spillman / A. Ibrahim / S. Hirschfeld

The Complete Remission (CR) was defined using conventional criteria in study PLRXAS01 as:

> *Cellular bone marrow aspirate with < 5 % blasts; Peripheral blood WBC ≥ 3000 /mm³ or ANC ≥ 1,500/mm³ and platelet count ≥ 100,000/mm³".*
> The bone marrow response must be maintained for at least 30 days.

According to CTI, patient with ID numbers 1005, 1023, 1024, 1034, 1038 and 1050 should be counted as complete responders by the above definition.

FDA counted patients with ID numbers 1023, 1038, and 1050 as complete responders. The others are not included for the following reasons:

Pt ID	Data Summary	Reason why not counted as CR
1024	10/9/98: BM biopsy: suboptimal study. Bone marrow interpretation: abnormal 11/4/98: Bone marrow response noted.	• Durable response with marrow aspirate in 30 days not documented.
1034	1/4/99: response documented. 1/25/99: hypocellularity documented(20-30%).	• Durable response with marrow aspirate in 30 days not documented
1005		• This patient was excluded from those being evaluated for CR as already discussed in the meeting

Patient with ID#1050 will be included as a responder after review of the new data CTI submitted on September 5, 2000.

MESSAGE CONFIRMATION

09/08/00 12:04
ID=ONCOLOGY/DOPDP/ODE-I/CDER/FDA

O.	MODE	BOX	GROUP
922	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
09/08 12:03	00'36"	+2062708463	002/002	OK		0000

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 2	**Date:** September 8, 2000
Re: NDA 21-248 – Follow-up to August 31, 2000 meeting: Complete Responders	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• Comments:

Jennie:

APPEARS THIS WAY ON ORIGINAL

MESSAGE CONFIRMATION

08/11/00 13:40
ID=ONCOLOGY/DOPDP/ODE-I/CDER/FDA

NO.	MODE	BOX	GROUP
563	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
08/11 13:39	00'53"	+2062708463	003/003	OK		0000

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell **From:** Dianne Spillman

Fax: (206) 270-8463 **Fax:** (301) 594-0499

Phone: (206) 270-8424 **Phone:** (301) 594-5746

Pages (including cover): 2 **Date:** August 11, 2000

Re: NDA 21-248 – Clinical Pharmacology & Biopharmaceutics (CPB) Information Request #3

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

PHASE 4 COMMITMENTS – Clinical Pharmacology & Biopharmaceutics

1. {

}

2. Conduct an *in vitro* study to assess the inhibition potential of arsenic trioxide on the major cytochrome P-450 isoenzymes.

3. From the limited pediatric pharmacokinetic information provided in this NDA (n=3), it is possible that the pediatric patients may exhibit higher exposure to arsenic trioxide than the adult population. Since you are seeking approval of the drug for a general patient population, and the pharmacokinetics of arsenic trioxide in the pediatric population is unknown, a formal pharmacokinetic study should be conducted in an appropriate number of children to adequately characterize the pharmacokinetics of arsenic trioxide in the pediatric population. Alternatively, this information can also be obtained from a pediatric efficacy trial using a prospectively planned population pharmacokinetic approach. We refer you to our published document titled "*Guidance for Industry, Population Pharmacokinetics*".

4. Characterize the pharmacokinetics of arsenic trioxide after administration of 0.15 mg/kg/day of arsenic trioxide in APL patients. Control patients enrolled in the renal and hepatic impaired patient study (see below) may also provide this information.

5. Because inorganic and organic arsenic are primarily excreted via the kidneys, patients with renal impairment are likely to have a different disposition pattern than the patients with normal renal function. Please conduct a pharmacokinetic study of arsenic trioxide in patients with varying degrees of renal function. We refer you to our published document titled "*Guidance for Industry, Pharmacokinetics in Patients with Impaired Renal Function*" for guidance on study design, categories of renal impairment, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

6. Since liver is the major site of methylation (detoxification) reactions for arsenic trioxide, accumulation of arsenic trioxide in hepatically impaired patients may occur upon chronic administration of the drug. Please conduct a pharmacokinetic study in hepatically impaired cancer patients. We refer you to our draft document titled "Guidance for Industry, Pharmacokinetics in Patients with Impaired Liver Function" for guidance on study design, categories of renal function, and data analysis for conducting such study. Please submit your protocol to the Agency for review.

7. Data from the all the pharmacokinetic studies conducted as a Phase IV commitment should be analyzed to evaluate the influence of age, gender, and race on the pharmacokinetics of arsenic trioxide.

APPEARS THIS WAY
ON ORIGINAL

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** July 27, 2000
Re: NDA 21-248 – Clinical Information Request #8	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Here's another clinical information request related to transfusions:

In the PLRXAS01 Study, pt ID 1015, 1019, 1029, 1031, 1033, 1036, 1038, 1040, 1042, 1046, 1050, 1051, 1052 received transfusions 'prn' or 'intermittently'. The start day and stop days are also different from each other. In some of these patients, ranges to be transfused are given, such as 1-4 u, prn. This makes it appear that the patients received more than the stated amounts of transfusions, since they were administered prn over several days. Are the absolute amounts transfused to the above patients known? If so, what are they?

Sincerely,

/S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/Div File/D. Spillman/A Ibrahim/S. Turschfeld

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** July 21, 2000
Re: NDA 21-248 – Clinical Information Request #7 (cardiology)	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Your fax of July 17th included the Barbey analysis of the first and second cycles of Trisenox as requested during our July 6, 2000 teleconference and July 17, 2000 fax. However, the actual QT and QTc values at baseline and steady-state for all of the patients included in the analysis (you summarize only the changes from baseline at each treatment period) were not provided.

The key question is whether the QT returns to baseline after treatment, or whether there is a long-term/permanent increase in QT. Please provide the values so that each patient's baseline and peak QTc values can be compared between treatment cycles. Thank you.

Sincerely, /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/Div Files / D.Spillman A.Ibrahim/S.Hirschfeld

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** July 18, 2000
Re: NDA 21-248 – Clinical Information Request #6	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☑ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Here is the request from Dr. Amna Ibrahim that we discussed briefly this morning:

There are no blood transfusions recorded for patients 1023, 1027, 1041 and 1047. Do you have no record of these, or did these patients not receive any blood products?

Also, patient 1030 in the ASO1 study did not have amounts of blood products transfused, written accurately. Please clarify the amounts.

Sincerely, /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

CC: NDA 21-248
HFD-150 / Div Files
/D. Spillman (for Action Pkg)
/A. Ibrahim
/S. Hirschfeld

MESSAGE CONFIRMATION

07/18/00 14:58
ID=ONCOLOGY/DOPDP/ODE-I/CDER/FDA

NO.	MODE	BOX	GROUP
215	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
07/18 14:58	00'24"	+2062708463	001/001	OK		0000

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell **From:** Dianne Spillman

Fax: (206) 270-8463 **Fax:** (301) 594-0499

Phone: (206) 270-8424 **Phone:** (301) 594-5746

Pages (including cover): 1 **Date:** July 18, 2000

Re: NDA 21-248 – Clinical Information Request #6

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☑ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** July 17, 2000
Re: NDA 21-248 – Clinical Information Request #5 (Cardiology Issues)	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Following my discussion w/ Dr. Barbey of Georgetown this morning, the following page of this fax clarifies the information expected from CTI as agreed during the July 6, 2000 teleconference.

Please provide the outstanding information (identified in bold font) as soon as possible. Thank you.

Sincerely,

/S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150 /Div Files
/D Spillman (for Action Pkg)
/A Ibrahim
/S Hirschfeld

Information to be submitted to FDA:

1. **Barbey report on first and second cycle ECGs.**

   This report includes the supplemental analysis performed on baseline and serial ECGs for 15 men and 9 women.

2. **All ECGs for patients receiving BMT or maintenance treatment.**

   If CTI performed an analysis comparing the QT intervals for the BMT vs. maintenance patients, please provide this information. If not, the Division does not expect CTI to conduct any additional analyses.

3. Initiation date of the first maintenance cycle, for any patient who received maintenance treatment. [response submitted in July 10, 2000 NDA amendment]

4. **Of the original 1000 ECGs, all ECGs for patients with a prolonged QTc.**

5. Location of the peak/trough blood level data in the NDA.
   [response submitted in July 10, 2000 NDA amendment]

6. **Fluid management (DLT outside the APL setting) definition for Division to consider as part of labeling.**

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 2	**Date:** July 10, 2000
Re: NDA 21-248 – OPDRA tradename consult result & CMC Information Request #2	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

As relayed earlier today, the Office of Postmarketing Drug Risk Assessment (OPDRA) has no objections to the use of the proprietary name "Trisenox".

Included with this facsimile transmission are two OPDRA recommendations regarding the container and carton label and the CMC review team's recommended wording for product storage conditions as it should appear on the package insert and carton/container label.

Sincerely /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/Div Files/D. Spillman
/C. Liang/X. Chen/E. Duffy

OPDRA

The following are OPDRA recommendations for labeling revisions to minimize potential errors with the use of this product.

CONTAINER LABEL (10 mL) and CARTON LABELING (10 x 10 mL)

1. The expression of strength should be revised on all labels and labeling to indicate the total contents of the ampule. We suggest the following:

   10 mg/10 mL
   (1 mg/mL)

2. Important information such as the drug name and strength should have the greatest prominence on the container labels and carton labeling. The company logo "cti" appears to have greater prominence on the labels and labeling than the proprietary and established names. We suggest the labels and labeling be revised to decrease the amount of space devoted to the corporate logo.

CMC

The CMC review team recommends the following storage conditions for inclusion on the package insert and carton/container labeling:

"Store at 25°C (68°C); excursions permitted to 15 - 30°C (59 to 86° F)."

Note, the above wording is slightly modified from the wording originally relayed in the June 22, 2000 facsimile below:

"Store at 25°C +/- 2°C, Excursions Permitted to 15 - 30°C (59 to 86° F).

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Jennie Allewell, CTI
Fax: 206 270-8463

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 1

Date: 6-29-00

COMMENTS: Re: your NDA 21-248 for [redacted] we have the following request:

Please submit the dates for initiation of maintenance therapy with Arsenic Trioxide after induction and consolidation for APL.

Thanks

Dotti for Dianne

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane; Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** June 21, 2000
Re: NDA 21-248 – Clinical Information Request #4 (Cardiology)	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

We issued a consult to our colleagues in the Cardio-Renal Division. They are in the midst of their review and asked if you could provide the following information as it relates to the ECGs that were conducted on the patients.

1. When were the ECGs taken relative to the infusion of [redacted] (that is, before, during or after)?
2. What is the effect of [redacted] on heart rate?
3. How was the QT corrected, and what was the definition of prolonged QTc used by the investigators?

Please provide this information as soon as possible. Thank you.

Sincerely, /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc NDA 21-248
HFD-150/Div File/D. Spillman/A. Braham/S. Hirschfeld

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell c/o Carolyn Paradise	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424 / (206) 378-4229	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** June 15, 2000
Re: NDA 21-248 – Clinical Information Request #3	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• Comments:

Jennie:

Please provide the following information:

1. Please identify by patient ID numbers, the patients who received maintenance treatment with Arsenic trioxide and the number cycles that each patient received.

2. According to FDA evaluations, patient 1023 met CR criteria. His bone marrow biopsy documenting CR was obtained on 9/16/98, and confirmatory bone marrow biopsy was done on 10/21/98. Required ANC and platelet count was documented on 10/16/98. Please explain why he was not included in your list of confirmed responders.

3. Patient number 1038 was electronically reported to have had a bone marrow biopsy on 9/23/99. There is no CRF for this in the NDA. Please submit this Case report form.

As to your inquiry on how to submit the latest survival data, this information can accompany the 3-month safety update submission. Feel free to amend the package insert to incorporate the updated survival data; however, since most of the reviewers have already initiated their labeling reviews, please include statements, in the cover letter, as to the specific changes and package insert sections affected by this data. Thank you!

Sincerely,

/S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc NDA 21-248
HFD-150/Div Files/D Spillman/A. Ibrahim/S. Hirschfeld

MEMO TO THE FILE

NDA #: 21-248 **DATE:** June 6, 2000

PRODUCT NAME: ( )(arsenic trioxide) **SPONSOR:** Cell Therapeutics Inc. (CTI)

SUBJECT: Safety Update Submission

Given the Division's target goal for a 4 month approval, Bob Temple (ODE 1 Director) suggested that I ask CTI to submit the 120-day safety update before the usual 4-month timeframe. I called CTI and asked whether they could submit the 120-day safety update at the end of June (3 months) instead of the end of July.

On June 2, 2000, I picked up a voice mail that Jennie Allewell (CTI) left on June 1, 2000. She indicated that CTI can submit the safety update the last week of June, but the safety update would include:

(1) An abbreviated integrated summary report without subanalyses.
(2) Full safety update on 52 patients.
(3) Serious adverse events on remaining patients beyond the 52 patients.
(4) A commitment to provide the full report on the extension study AS02 after approval.

CTI asked for comment on their proposed safety update submission and noted that they will provide all the information they have available at the time of the 3-month safety update.

I sent an e-mail to the clinical team on June 6, 2000 and the medical officers, Drs. Steven Hirschfeld and Amna Ibrahim found CTI's safety update proposal acceptable.

I called and left a voice mail message with Jennie Allewell, CTI, at 1:58 p.m. on June 6, 2000 and informed her that their safety update proposal is acceptable and that we expect their safety update at the end of June 2000.

/S/
Dianne Spillman
Project Manager, HFD-150

cc: NDA 21-248
HFD-150/Division File
/D.Spillman
/A.Ibrahim
/S.Hirschfeld

MEMO TO THE FILE

NDA #: 21-248 **DATE:** June 6, 2000

PRODUCT NAME: [redacted] (arsenic trioxide) **SPONSOR:** Cell Therapeutics Inc. (CTI)

SUBJECT: Clinical Pharmacology & Biopharmaceutics Information Request – Missing appendices

---

The Clinical Pharmacology and Biopharmaceutics reviewer, Dr. Safaa Ibrahim, noted that appendix D was missing from the 1.15 technical volume (also known as Item 6, volume 5). She asked me to retrieve the archival volume from the Central Document Room. It appeared that the archival volume also did not have appendix D, nor did it have appendices E and F.

I called Jennie Allewell of CTI on June 2, 2000 and asked them to provide, as soon as possible, the missing appendices from volume 1.15 (or Item 6, volume 5) as an NDA amendment.

On June 5, 2000, I picked up a voice mail that Jennie Allewell (CTI) left on June 2, 2000. She said that appendices D, E, and F were actually on pages 051, 052 and 053, respectively of volume 1.15 under the tab titled "Item 6 Section 6.6 Appendices". Ms. Allewell noted that tabs with the alphabetic headings contained the references and not the appendices, and that this probably contributed to the confusion.

I relayed this information to Dr. Ibrahim on June 5, 2000.

I called Jennie Allewell of CTI on June 6, 2000 and left a voice mail message noting that CTI need not submit anything to the NDA related to this information request.

/S/

Dianne Spillman
Project Manager, HFD-150

cc: NDA 21-248
HFD-150/Division File
/D.Spillman
/S.Ibrahim

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** June 1, 2000
Re: NDA 21-248 – Clinical Information Request #2	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Please provide the following information for patients in the PLRXAS01 study:

1. The dates of diagnosis, relapse, initiation and discontinuation of treatment. Currently, many patients have some of these missing.

2. The missing values for PT, PTT, Fibrinogen, D Dimer, FDP, as well as the normal or control ranges for these tests.

Sincerely,

/S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/DivFiles
/D. Spillman
/A. Ibrahim/S. Hirschfeld

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** May 5, 2000
Re: NDA 21-248 – Clinical Information Request	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

Please provide patient ID's for those 4 patients that had QT prolongation greater than 500 msec on EKG's. Thank you.

Sincerely,

/S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

APPEARS THIS WAY
ON ORIGINAL

5/5/00 555 pm
In J. Allewell's absence, called C. Paradise (206) 378-4229, to relay info request. C. Paradise said she'd fax me patient IDs – only 3 patients, 4th EKG is for one of the 3 – by today.

5/5/00 558 pm
C. Paradise called to say EKGs list pt IDs @ top. I checked submission and the fact that EKGs are jacketed does not allow us to more easily see pt ID. ∴ C. Paradise

cc: NDA 21-248
HFD-150 /Div Files
/D. Spillman
/A. Ibrahim /S. Hirschfeld

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** April 20, 2000
Re: NDA 21-248 – Clinical Pharmacology & Biopharmaceutics (CPB) Information Request #2	

☐ **Urgent** ☒ **For Review** ☐ **Please Comment** ☒ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

The CPB reviewer asks that you provide some information as to which of the following species: inorganic, methyl metabolites, or organic, is the active species in [redacted] and how much each species contributes to the overall activity of the drug.

Sincerely, /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/DivFiles
/D.Spillman
/S.Ibrahim
/Huru A.Rahman 4.20.00

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Jennie Allewell	**From:** Dianne Spillman
Fax: (206) 270-8463	**Fax:** (301) 594-0499
Phone: (206) 270-8424	**Phone:** (301) 594-5746
Pages (including cover): 1	**Date:** April 12, 2000
Re: Information Request – Clinical pharmacology & biopharmaceutics (CPB)	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:**

Jennie:

As promised yesterday afternoon, this fax serves as written documentation for your files and details the request from the CPB reviewer.

> The package insert contains information that is not supported by data in the NDA submission. In order to evaluate the claims in the package insert, please provide the data, or direct us to the data location in the NDA, regarding (1) protein binding studies, (2) RBCs binding studies, (3) in vitro and vivo metabolism, and (4) excretion (with radiolabeled drug).

Please provide this information as soon as possible, preferably before the Division filing meeting scheduled for May 12, 2000. As discussed, when you respond to any information requests from the Division, please send me the cover letter via fax, followed by the official amendment to the NDA. Thank you.

Sincerely, /S/

Dianne Spillman, Project Manager
Division of Oncology Drug Products

cc: NDA 21-248
HFD-150/Div Files
/D.Spillman
/S.Ibrahim/A.Rahman

cti

Discovery • Treatment • Recovery

T 206 282 7100 F 206 284 6206

ORIGINAL NEW DRUG APPLICATION

March 27, 2000

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkens Ave.
Rockville, MD 20852

Re: **NDA 21-248**
Application for [redacted] (arsenic trioxide injection) for the treatment of acute promyelocytic leukemia (APL)

Dear Sir or Madam:

Cell Therapeutics Inc. (cti) is submitting this original submission of the New Drug Application (NDA) for [redacted] (arsenic trioxide injection). The proposed indication for [redacted] is for the induction of remission and consolidation in patients with relapsed or refractory acute promyelocytic leukemia (APL), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RAR (alpha) gene who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. cti proposes to market [redacted] as a prescription product.

[redacted] (arsenic trioxide) injection has been designated as a fast track product for the treatment of APL on February 25, 2000 (copy of FDA Designation letter provided following 356h form). At this time, cti respectfully request that this NDA 21-248 be considered for priority review.

The clinical development program for arsenic trioxide (ATO) involved 132 patients with a variety of malignancies (hematologic and non-hematologic solid tumors) who were enrolled in 11 studies. These studies provided evidence of clinical efficacy and safety in patients with APL, provided supportive pharmacokinetic information in both patients with APL and with other malignancies, and provided information regarding the general safety of ATO in patients with a variety of malignancies. The studies that comprised the efficacy and safety data were conducted under [redacted] one by Memorial Sloan Kettering Cancer Center (MSKCC) and one by PolaRx Biopharmaceuticals Inc (PolaRx). A cross-reference letter for the MSCKK [redacted] is provided in this application. On Janurary 10, 2000, PolaRx was acquired by cti and is now a wholly owned subsidiary.

On March 9, 2000, the sponsorship of the PolaRx was transferred from PolaRx to cti.

Arsenic trioxide was granted orphan drug designation for the treatment of acute promyelocytic leukemia on March 3, 1998. The orphan designation was transferred from PolaRx to cti on March 10, 2000.

The clinical development of ATO was the subject of two meetings with FDA/CDER/DODP, an end-of Phase 2 meeting on April 14, 1998 and a pre-NDA meeting on January 6, 2000. Based on agreements reached at each of these two meetings, this original submission contains two pivotal studies that provide the primary safety and efficacy data for the target population (APL): a Phase I/II study, 97-66, conducted under the MSKCC and a Phase II/III study, PLRXAS01, sponsored by PolaRx. Two extension studies, 98-13 and PLRXAS02, allowed additional maintenance therapy for patients who achieved a complete response in the 2 pivotal studies and provided additional safety information. Two Phase I/II and 2 Phase II studies were conducted in patients with other malignancies (hematologic and solid tumor), under both the MSKCC and the PolaRx

The drug substance is manufactured for cti by:

The drug product is manufactured for cti by:

labels and packages at their packaging facility at the following address:

This NDA submission is organized according to FDA's guidance document titled "Guidelines on Formatting, Assembling, and Submitting New Drug and antibiotic Applications (February 1987) and according to the requirements listed in the 21 CFR 314.50. Each page is numbered by item, volume number, and page number within each

volume (i.e., the NDA is not sequentially numbered from start to finish). The item number, volume number, and page number are indicated in the lower right hand corner of each page. e.g., 4VOL2 P006 (i.e., Item 4, volume 2, page 6).

As agreed upon with the Division in the pre-NDA meeting held on January 6, 2000, the entire archival copy is submitted in paper format. The review copy consists of the 6 technical sections (Chemistry, Nonclinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailability, Microbiology, Clinical, and Statistics). In addition, 6 copies of "Volume 1" of the NDA are enclosed so that each technical reviewer can have his or her own copy. "Volume 1" consists of this cover letter, Form FDA 356h, Index (e.g., the overall Table of Contents), Draft Labeling, Summary for the New Drug Application, and Items 13, 14, 15, 16, 17, 18, and 19. The NDA consist of 82 volumes as follows:

Item	Number of Volumes
1. Index	*
2. Draft Labeling	*
3. Summary of NDA	*
4. Chemistry Section	4
5. Nonclinical Pharm/Tox	5
6. Human PK and Bioav.	6
7. Microbiology	1
8. Clinical Data	16
10. Statistical Section	15
11. Case Report Tabulations	9
12. Case report Forms	25
13. Patent Information	*
14. Patent Certification	*
15. Establishment Desc.	*
16. Debarment Certification	*
17. Field Copy Certification	*
18. User Fee Cover Sheet	*
19. Other	*

* These 10 Items are bound together in a single "Volume 1".

Please be advised that 2 review copies of the technical Items 4 and 6 are provided, and also an additional copy of Item 4, volume 4 (Samples and Methods Validation Package).

The clinical database, statistical analysis files, and datasets for Study Nos. 97-66 and PLRXAS01 are provided in electronic SAS transport format in compliance with the requirements described in the Guidance for Industry—Providing Regulatory Submissions

in Electronic Format – NDAs (January 1999). This information is contained in one CDROM (163 Megabytes), secured in a plastic sleeve, located in the front of volume 1 of Item 10: Statistical Section.

In addition, as agreed upon at the pre-NDA meeting, the following data are also being submitted in electronic format as reviewer aids: study protocols, study reports, draft product label, list of investigators with study site name, number of patients at each site and number of patients who went into remission at each site, patient data tabulations including for all study patients and all historical control patients, previous therapy with start and stop dates and date of relapse, and complete safety data. The electronic information is provided in PDF file format as a courtesy copy for reviewer aids in addition to the paper copy of the NDA, but is not created in accordance with the Guidance for Industry—Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). Each CDROM contains the PDF files; one for each volume of the paper Item. These files are named as Item X VolumeX.pdf, mirroring the paper submission. One CDROM each containing the electronic information is provided for Item 6 (78.7 Megabytes), Item 8 (134 Megabytes), Item 10 (118 Megabytes), and Item 11 (9.7 Megabytes). The PDF files on CDROMs are secured in plastic sleeves, located in the front of volume 1 of the appropriate technical section except for Item 11 CDROM (containing the Case Report Tabulations) which is located in the front of Item 8, volume 1.

By this letter, cti certifies that the information being submitted in electronic format is virus free. The McAfee VirusScan 4.0.3A [Version 4.0.4068 (March 8,2000); Network Associates, Inc.] was used to check the files for viruses.

Feedback was received from the Division on March 23, 2000 on the statistical analysis plans for the two studies 97-66 and PLRXAS01. The presentation of data requested has been incorporated into the Integrated Summary of Effectiveness (ISE) in volume 1 of Item 8: Clinical Data.

We look forward to the review of this original submission and appreciate your assistance on this project. Please call if you have questions or need additional information at 206-270-8424.

Very sincerely yours,

Jennie Allewell
Cell Therapeutics Inc.
Director, Regulatory Affairs and Compliance

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Cell Therapeutics, Inc.	March 27, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(206) 282-7100	(206) 270-8463
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 201 Elliott Ave West # 400 Seattle, WA 98119	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)
21-248

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
	(trademark pending)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
arsenic trioxide injection	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
small volume parenteral	1 mg/mL solution	intravenous infusion

(PROPOSED) INDICATION(S) FOR USE:
Provided on sheet attached

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 82 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Provided on sheet attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Feb. 7, 1992 pp. 2, 3, 4, 5, 6.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 21 2000

NDA 21-248

Cell Therapeutics, Inc.
201 Elliott Avenue West #400
Seattle, WA 98119

Attention: Jennie Allewell
Director, Regulatory Affairs and Compliance

Dear Ms. Allewell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [redacted] (arsenic trioxide injection) 1 mg/mL

Therapeutic Classification: Priority (P)

Date of Application: March 27, 2000

Date of Receipt: March 28, 2000

Our Reference Number: NDA 21-248

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 27, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 28, 2000.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Dianne Spillman, Regulatory Project Manager, at (301) 594-5746.

Sincerely,

/S/ 4-21-00

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 21-248
HFD-150/Div. Files
HFD-150/D.Spillman
HFD-150/J.Johnson
/S.Hirschfeld
/A.Ibrahim
/E.Duffy
/C.Liang
/X.Chen
/P.Andrews
/J.Leighton
/G.Chen
/P.Yang
/A.Rahman
/S.Ibrahim
DISTRICT OFFICE

final: dds/4-20-00

ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

[redacted]

PolaRx Inc.
787 Seventh Avenue
48th floor
New York, NY 10019

FEB 25 2000

Attention: Ralph Ellison, M.D.

Dear Dr. Ellison:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for [redacted] arsenic trioxide.

We also refer to your December 23, 1999 request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating [redacted] (arsenic trioxide) injection for the treatment of APL as a fast track product.

We are granting fast track designation for the following reasons:

1. Acute promyelocytc leukemia is a life threatening malignancy that can result in rapid death if not treated promptly.

2. The use of arsenic trioxide may result in remissions in patients who have not been able to attain remission using either cytotoxic agents or all trans retinoic acid. This could avoid the near certain rapid death of these patients.

If you pursue a clinical development program that does not support use of [redacted] (arsenic trioxide) injection for the treatment of APL, we will not review the application under the fast track development program.

If you have any questions, contact Ann Staten, Regulatory Project Manager, at (301) 594-5770.

Sincerely yours,

/S/

Robert Justice, M.D.
Deputy Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

March 3, 1998

PolaRx, Inc.
787 7th Ave., 48th Floor
New York, NY 10019

Attention: Ralph Ellison, M.D.
Chief Executive Officer

Dear Dr. Ellison:

Reference is made to your orphan drug application of December 4, 1997 submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act for the designation of arsenic trioxide as an orphan drug (application [redacted])

We have completed the review of this application and have determined that arsenic trioxide qualifies for orphan designation for the treatment of acute promyelocytic leukemia. Please note that it is arsenic trioxide and not its formulation that has received orphan designation.

Please be advised that if arsenic trioxide were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of arsenic trioxide as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Ms. Diane Centeno-Deshields at (301) 827-0980.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

19.1.2 Copy of PolaRx Letter to the Office of Orphan Drug Products dated March 10, 2000

POLARX INC
BIOPHARMACEUTICALS

RECEIVED

MAR 10 2000

Office of Orphan
Products Development

March 10, 2000

Marlene E. Haffner, M.D., M.P.H
Director
Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Re: Request for transfer of designation of [redacted] arsenic trioxide injection for the rare disease acute promyelocytic leukemia (APL)

Dear Dr. Haffner:

Pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) (U.S.C. 360bb), reference is made to the letter of March 3, 1998 in which PolaRx Biopharmaceuticals, Inc. (PolaRx) subsidiary of Cell Therapeutics, Inc. received the designation of "Orphan Drug" for its product [redacted] arsenic trioxide injection for the treatment of patients with acute promyelocytic leukemia (APL) (Reference [redacted]). Further reference is made to CTI's acquisition of PolaRx on January 10, 2000.

This submission requests that the designation of [redacted] for APL be transferred from PolaRx to Cell Therapeutics, Inc. (CTI) The contact person at CTI is Jennie Allewell, Director, Regulatory Affairs and Compliance, telephone number (206)-270-8424.

Cell Therapeutics, Inc. is planning to submit a New Drug Application for the use of arsenic trioxide for patients with APL in 1q 2000. Cell Therapeutics, Inc. will notify your Office within 30 days of submission of this marketing application.

If you have any questions or need additional information, please call me at 212-554-4362.

Sincerely yours,

Ralph Ellison, CEO
PolaRx Biopharmaceutical, Inc.
Wholly Owned Subsidiary of Cell Therapeutics, Inc.
201 Elliott Avenue West
Suite 400
Seattle, WA 98119